AMINOTHIOL COMPOUNDS AND ACYLATED DERIVATIVES THEREOF

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates aminothiol compounds and their acylated derivatives thereof which perform as superior catalysts in the asymmetric addition reactions of organic zinc and aldehyde.

2. Description of the Related Technology

For preparing secondary alcohols, one of the most important methods is to react organic zinc with aldehyde in addition reactions. In order to accelerate this reaction, chiral aminoalcohols are usually added as ligands to combine with organic zinc. Such chiral aminoalcohol create an asymmetric reaction environment, so that one of the produced chiral secondary alcohols is produced more than its stereoisomer, i.e., the asymmetric addition reactions. Apparently, the crux of obtaining a high chemical yield as well as enantioselectivity in the above reactions is to select proper chiral compounds which can provide excellent asymmetric environment for catalytical process.

Though many chiral compounds used in the addition reactions regarding organic zinc and aldehyde can achieve good enantioselectivity, however, these compounds have to be added at an amount at least 1% of the main reactants, and usually around 20%.

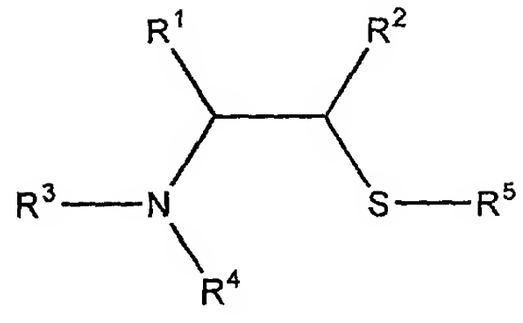
Additionally, the enantioselectivity always decays with decreasing amount of the chiral ligands used. In general, the enantioselectivity is reduced below 90% enantiomeric excess (e.e.) when the chiral ligands are descended under 5%, so that most of above reactions are not good enough for industrial usage.

Aminoalcohols with optical activity, such as N,N-dibutylnorephe- edine, are frequently applied to accelerating the asymmetric addition reactions of organic zinc and aldehyde as chiral ligand catalysts. By adding aminoalcohols, enantioselectivity of the above reactions can be reached as high as 99% e. e., but an amount 10-20% of chiral aminoalcohols is need. Therefore, it's an important issue how to reduce the necessary amount of the chiral ligands used in the catalysis, so that it can be an economically efficient process

SUMMARY OF THE INVENTION

The object of the present invention is to provide aminothiol compounds with two chiral centers and their acylated derivatives thereof, which can increase enantioselectivity of asymmetric addition of of organic zinc and aldehyde.

In order to achieve the above object, the present invention discloses the aminothiol compounds and their acylated derivatives thereof, which have general formula I and formula II, respectively;



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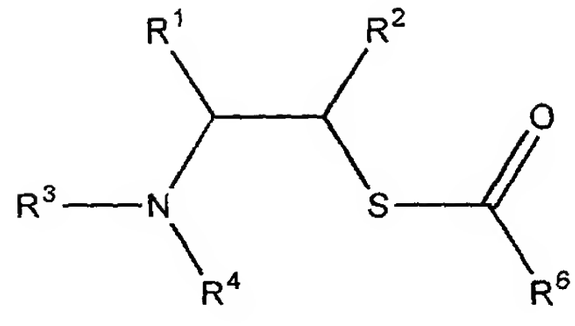


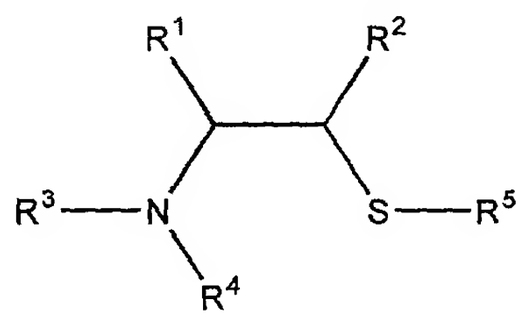
II

wherein R^1-R^6 are substitutable ligands.

According to the present invention, the aminothiol compounds and their acylated derivatives thereof can perform as superior catalysts in asymmetric addition reactions wherein organic zinc and aldehyde are involved, In such reactions, though the catalysts are added only 0.1% or even 0.02%, enantioselectivity higher than 99% e.e. can always be obtained. So that such catalyses are economically useful for industries.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

In the present invention, aminothiol compounds and their acylated derivatives thereof have general formula I and formula II, respectively,



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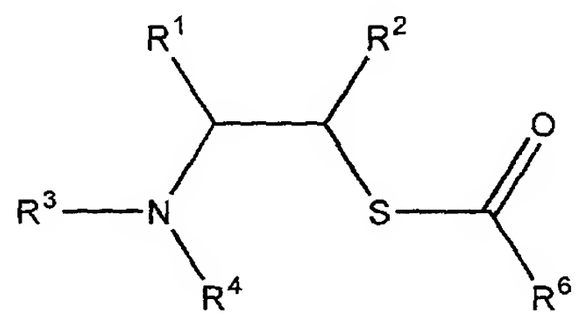


II

wherein R^1 is aryl or alkyl of C1-C9;

R^2 is aryl or alkyl of C1-C9;

R^3 is alkyl of C1-C9;

R^4 is alkyl of C1-C9;

or R^3, R^4 and N can form a three-to-eight-membered

heterocycle;

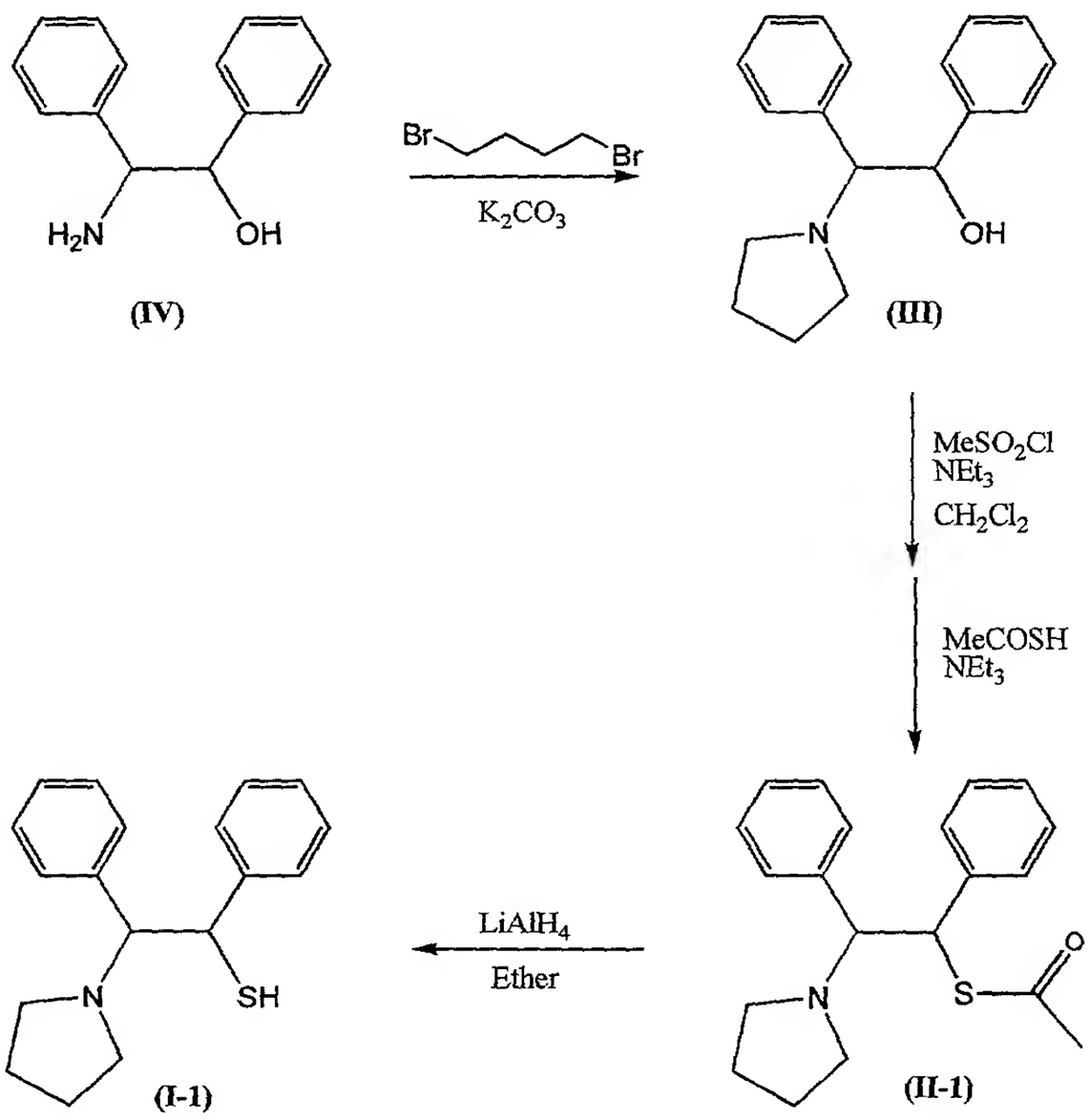
R^5 can be H or alkyl of C1-C6; and

R^6 can be H or alkyl of C1-C6.

A method for preparing the above ligands and application thereof are as follows:

1. Preparing the ligands

A typical compound of the present invention can be obtained according to the following scheme,



(IV) (III) (I-1) (II-1)

wherein the compound of formula I-1 is obtained by reacting the compound of formula II-1 with $LiAlH_4$ (lithium aluminum hydride).

This method includes steps of:

S11: $LiAlH_4$ and THF (Tetrahydrofuran) are added into a dried three-neck flask under a nitrogen system, the temperature is then regulated to 0 ℃, and the compound of formula II-1 disolved in THF is added into the flask through an auto-injector in 30 minutes.

S12: After the above reactants have completely reacted by stirring for one hour, 15 % aqueous NaOH is added to terminate the reaction.

S13: The solution of S12 is filtered through a filter paper, wherein the remained solid is repeatedly washed with a solvent and the filtrate is concentrated by reducing pressure through a vacuum pump to obtain coarse product.

S14: The crude product is then purified through flash column chromatography (Silica gel; eluent is Hex : Et_3N= 100 : 1) to obtain white solid.

Further, the compound of formula II-1 is produced by reacting (1*R*, 2*S*)-(-)-1,2-diphenyl-2-aminoethanol, i.e., the compound of formula IV, with 1,4-dibromobutane and potassium carbonate to produce the compound of formula III with the cyclic structure as morpholine

S21: The compound of formula III is dissolved in dichloromethane under nitrogen, then triethylamine is injected therein, and the temperature is reduced to 0℃.

S22: $MeSO_2Cl$ dissolved in dichloromethane is dropwisely added into the solution obtained in S21 through a funnel.

S23: After the above solution has completely reacted by stirring for two hours , the aliquote is concentrated by reducing pressure through a vacuum pump, benzene is added therein under nitrogen, and the mixture is heated and refluxed.

S24: Thiolacetic acid and triethylamine are dissolved in benzene and then injected into the mixture of S23.

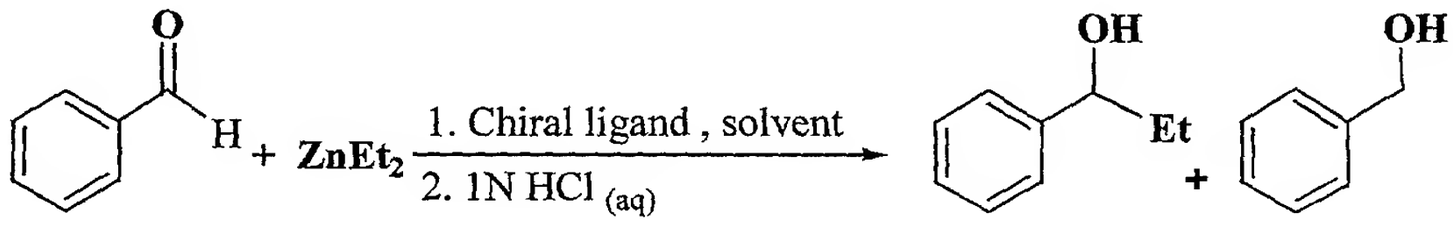
S25: After the above mixture has completely reacted by stirring for eight hours, H_2O is added therein to terminate the reaction, and the mixture is extracted with dichloromethane for three times.

S26: Anhydrous Na_2SO_4 is added into the organic layer obtained in S25 to absorb H_2O, which is then filtered and concentrated by reducing pressure through vacuum pump to obtain crude product.

S27: The crude product is purified by column chromatography (Silica gel, eluent is n-Hexane: EtOAc: Et_3N = 100: 1: 1) to obtain a yellow liquid, i.e., the compound of formula II-1.

2. Application of the present invention

The addition reaction of organic zinc and aldehyde can be shown as the following scheme.



The above scheme includes steps of:

S31: The ligand of formula I-1 (0.03 g, 0.1 mmol) and a dried magnetic stirrer are added into a dried flask.

S32: The flask is sealed and vacuumed to remove moisture and then filled with nitrogen, and then diethylzinc (1.10 mL, 1.2 mmol) is added therein at room temperature and stirred for two hours.

S33: The temperature is adjusted to -20℃, and benzaldehyde (0.11 mL, 1.0 mmol) is added therein and stirred for 12 hours.

S34: 1N aqueous HCl (1 mL) is added into the above solution to terminate the reaction.

S35: The solution of S34 is extracted with acetyl acetate (20 mL), wherein the organic layer is collected and dehydrated with anhydrous $MgSO_4$, and then the mixture is filtered, and the filtrate is concentrated by reducing pressure through an air pump to obtain crude product.

S36: The crude product is purified by column chromatography (Silica gel, eluent is n-Hexane: EtOAc = 10: 1).

In order to confirm that high enantioselectivity can be obtained from the present invention, different aminothiol compounds (4d4c, 2b4b, 5d5c) are provided to perform the reactions. The results are listed in Table 1, in which only few values of enantioselectivity are lower than 99% e.e. when the amount of these ligands is 0.02%. Additionally, when the amount of these ligands is 0.1%, all values of enantioselectivity are higher than 99% e.e.

Obviously, the aminothiol compounds and the acylated derivatives therof in accordance with the present invention are superior than the catalysts exsiting in the literature for the asymmetric addition of organic

zinc to aldehyde. In such reactions, though the catalysts are added only 0.1% or even 0.02%, enantioselectivity higher than 99% e.e. are always obtained. Therefore, aminothiol compounds and acylated derivatives thereof in the present invention are indeed very economic for applying the above asymmetric reactions to industries.

Similarly, the aminothiol compounds and their acylated derivatives thereof in the present invention can be provided as chiral ligands to react with other organic metals, for example, Cu, Ti, etc., to form organometal complexes. These complexes can also react with carbonyl such as aldehyde and ketone, to produce alcohol in the asymmetric addition reactions.

It should be noticed that the above embodiments are only used for explaining the present invention, but not limiting the scope.